P2-003 BSTB: Cancer Genetics Posters, Tue, Sept 4

Increased vascular-endothelial growth factor A (VEGF-A) expression and response to angiogenesis inhibitor erlotinib in non-small-cell lung cancer (NSCLC) - Hint for a new predictive marker?

Brueckl, Wolfgang M.[1] Wirtz, Ralph M.[2] Schoeberl, Anja[1] Murray, Samuel[3] Hahn, Eckhart G.[1] Wiest, Gunther H.[1]

[1] Dept of Medicine 1 University Hospital Erlangen, Erlangen, Germany [2] Siemens Medical Solutions, Leverkusen, Germany [3] Dept of Molecular Biology Metropolitan Hospital, Athens, Greece

Background: Non-small-cell lung cancer (NSCLC) is the most common cancer in the world and prognosis is poor. Recently, erlotinib, an epithelial growth factor receptor (EGF-R) tyrosine kinase inhibitor has shown to be effective in terms of survival in second/third-line chemotherapy. However, the overall response rate is about 9%. Somatic mutations of the EGF-R gene or amplifications of the EGF-R gene seem to be associated with response to erlotinib.

Methods and Results: We report about a young non-smoking Caucasian woman with metastastic NSCLC progressive to first-line platin-based combination therapy. She had a good partial response to erlotinb as second line therapy lasting over 6 months. By sequencing exons 19-21 of the EGF-R gene and the K-RAS gene, there was no somatic mutation detectable in the tumour or in a liver metastasis. Additionally, using chromogenic in situ Hybridisation (CiSH) there was no EGF-R amplification found in the tumour or metastasis. However, we found a VEGF-A mRNA overexpression in the primary lung tumour and liver metastasis in comparisson to normal lung epithilium. VEGF-A overexpression was confirmed at the protein level by immunohistochemistry.

Conclusions: These findings contribute to the hypothesis, that there might be an association between the EGF-R and VEGF pathways. Furthermore, VEGF expression might be another marker for response to erlotinib therapy in NSCLC. To further analyse this potential predictive factor, VEGF expression should be studied systematically in responders to erlotinib therapy.

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MicroRNAs in human lung cancer and human lung embryogenesis

Carcereny, Enric[1] Gallardo, Elena[1] Navarro, Alfonso[2] Gel, Bernat[2] Jansa, Sonia[2] Marrades, Ramon[3] Ramirez, Josep[4] Casas, Francesc[5] Viñolas, Nuria[6] Monzó, Mariano[7]

[1] Department of Oncology, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain [2] IDIBAPS, Barcelona, Spain [3] Department of Pneumology, Hospital Clínic i provincial de Bracelona, Barcelona, Spain [4] Department of Patology, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain [5] Department of Radiotherapy, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain [6] Department of Oncology.,Hospital Clinix i Provincial de Barcelona, Barcelona, Spain [7] Department of Anatomy, Faculty of Medicine. University of Barcelona, Barcelona, Spain

Aim: To analyze if the miRNAs present in lung embryogenesis are also active in lung tumors and which are differentially expressed between tumor and normal lung tissue.

Methods: We studied by Real Time-PCR 18 mature miRNAs (let-7a family, cluster 17-92, mir-155, RNU6B, RNU66) in lung tissue from twelve 7-12-week human embryos and 36 human lung samples (18 tumor and 18 normal). Data were analyzed with BRB Array tools and TIGR M-Viewer.

Results: The hierarchical clustering showed four groups: E7-8 embryos, E9-12 embryos, tumor and normal samples. Embryonic samples were closer to tumor samples. To determine common miRNAs during tumor and embryonic development, we analyzed the miRNAs differentially expressed between tumor and embryonic tissues versus normal. miRNAs mir-17-5p, mir-106a, mir-19a, mir-25, mir-93 and mir-98 were overexpressed in tumor and embryos samples and miRNAs let-7a, let-7b, let-7c and let-7g were underexpressed compared to normal samples.

We analyzed the miRNAs differentially expressed between tumor and normal samples and we found that mir-106a, 93, 17-5p, 25, mir-98 and mir-19a were significantlly overexpressed and let7-a, let-7c, let-7g and let-7b were significantlly underexpressed. These miRNAs allows to classify a sample as tumoral or normal.

Conclusions: Due to their similar expression miRNAs of cluster-17-92 and members of let-7 family play a role during the normal lung and tumor development. These miRNAs may be a good targets for new therapeutics strategies.

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Expression networks regulated by gene dosage in lung adenocarcinoma

Chari, Raj[1] Coe, Bradley P.[1] Ng, Raymond T.[2] MacAulay, Calum[1] Yee, John[1] English, John C.[1] Lam, Stephen[1] Lam, Wan L.[1]

[1] British Columbia Cancer Agency, Vancouver, BC, Canada [2] University of British Columbia, Vancouver, BC, Canada

Background: Adenocarcinoma (AC) is the most common lung cancer cell type in many countries. Identification of genes such as EGFR has demonstrated the importance of defining primary pathway alterations for the development of new AC treatments. However, genes altered at the expression level may be a result of reactive changes through complicated regulation by other genes. Thus, genes whose expression is regulated by alterations in gene dosage (copy number) are attractive targets for therapeutic intervention as they likely represent the primary alterations in cancer development.

Methods: We integrated high resolution copy number profiles (whole genome SMRT array CGH) for 20 cell lines and 27 primary tumors, with Affymetrix [Cancer Cell 2006 Jul 10(1):39-50] and custom Agilent (tumors) expression data. The Mann Whitney U test was used to identify copy number regulated genes in both sample sets and genes identified in both cell lines and tumors were isolated for further analysis. Pathway based analysis and integration of publicly available survival study results [Nature Medicine 2002 Aug 8(8):816-24] were performed with Ingenuity Pathway Analysis software.

Results: Comparison of copy number and expression profiles in complimentary sets of cell lines and primary tumour samples identified 458 genes which appear to be causally regulated by copy number alteration in AC. Integration of our new findings with survival data correlated genes generated a striking overlap in the disruption of cellular pathway functions between the two data sets. These results can explain the disruption of survival correlated functions by primary copy number induced deregulation.

Conclusions: Integration of gene expression and copy number data delineated genetic alterations that are correlated with outcome. The identified genes may serve as prognostic markers and therapeutic targets